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Clinical trial

Comparative trial of a novel botulinum neurotoxin type A versus onabotulinumtoxinA in the treatment of glabellar lines: A multicenter, randomized, double-blind, active-controlled study

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Abstract

A novel botulinum neurotoxin type A (DWP450; Daewoong Pharmaceutical, Seoul, Korea) has recently been introduced for the treatment of facial wrinkles. The efficacy of this agent has previously been demonstrated in an *in vivo* study using an electrophysiological protocol in a rat model. To compare the efficacy and safety of DWP450 with onabotulinumtoxinA (OBoNT) for use in the treatment of glabellar lines, we performed a multicenter, double-blind, randomized, active-controlled trial comparing DWP450 and OBoNT (Allergan Inc., Irvine, CA, USA). A total of 268 subjects with moderate to severe glabellar lines were randomized at a 1 : 1 ratio. Each patient received treatment with 20 U of study medication. Maximum frown responder rates at week 4 were measured to analyze the primary efficacy endpoint. To evaluate secondary efficacy endpoints, response rates were measured at weeks 8, 12, and 16, at maximum frown and rest. Specifically, responder rates at both maximum frown and at rest were assessed based on clinical photography. Subject degree of satisfaction and self-assessed rate of response were also measured. Adverse events (AEs) were documented to evaluate safety. Responder rate by physician-rating severity at maximal contraction at week 4 was 93.89% in the DWP450 group and 88.64% in OBoNT group. As the lower limit of the 97.5% one-sided confidence interval (– 1.53%) surpassed the – 15% threshold, we determined that DWP450 was not inferior to OBoNT. For the secondary efficacy endpoint analyses, no significant differences were observed between the two groups for any variable at any point in time. The incidences of AEs were similar for the two groups. Most of AEs were considered mild. DWP450 and OBoNT were comparable in efficacy and safety in the treatment of glabellar lines.

Introduction

Botulinum toxin has long been safely and effectively used to treat various disorders associated with undesirable muscle hyperactivity, including blepharospasm, focal dystonia, and hemifacial spasm.[1] Recently, the use of this agent has rapidly expanded in the field of aesthetic medicine. In particular, botulinum neurotoxin type A (BoNT-A) has been approved for the treatment of glabellar lines and lateral canthal lines (crow's feet) by the US Food and Drug Administration (FDA), with numerous studies demonstrating the efficacy and safety of this agent in the treatment of facial wrinkles, including horizontal lines on the forehead, crow's feet, and glabellar rhytides.[2–4]

DWP450 (Daewoong Pharmaceutical, Seoul, Korea), a new BoNT-A formulation, was introduced recently. DWP450 (Daewoong botulinum toxin type A) originated from wild-type *Clostridium botulinum* presents higher purity of BoNT-A, which confirmed by size exclusion high-performance liquid chromatography analysis showing a single 900 kDa peak (>98%) in comparison with 95% of purity in onabotulinumtoxinA (OBoNT). In a previous *in vivo* study, we demonstrated that DWP450 produces an effect similar to that of OBoNT using a

split-body electrophysiological protocol in a rat model.[5] Also in the comparative toxicology study, DWP450 showed two times higher safety than that of OBoNT (DWP450 NOAEL was 60 U/kg of female SD rat and OBoNT was 30 U/kg of female SD rat). As there has been no information about the clinical efficacy or safety of DWP450, we performed a multicenter, randomized, double-blinded, active-controlled trial to compare DWP450 and OBoNT in the treatment of glabellar lines. Based on our previous animal experimental results, in this study, we formulated two clinical hypotheses: DWP450 has an acceptable efficacy and safety profile in treating glabellar lines, and the efficacy of DWP450 is not inferior to that of OBoNT at a 1 : 1 dose ratio.

Materials and methods

Study design

This prospective, double-blinded, randomized, active-controlled study was conducted in three medical centers (Chung-Ang University Hospital, Ulsan University Asan Medical Center, and St. Paul's Hospital, Catholic University, Seoul, Korea). Before initiation, the study protocol was reviewed and approved by the institutional review board at each institution. Written consent from all participants was obtained using an institutional review board approved form before enrollment.

Study population and randomization

The participants were recruited from three centers. To qualify for study enrollment, participants needed to be between 20 and 65 years of age and exhibit glabellar lines of at least moderate severity at maximum frown (graded on a four-point facial wrinkle scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe). Subjects with any condition that could cause neuromuscular junction dysfunction (such as myasthenia gravis, Lambert–Eaton myasthenic syndrome, amyotrophic lateral sclerosis, or any systemic neuromuscular junction disorder) were excluded. Other exclusion criteria included the use of aminoglycosides, curare-like agents, or muscle relaxants in the four weeks preceding the start of the study, or previous aesthetic procedures in the six months preceding the start of the study.

At each center, eligible patients were randomly assigned to either the DWP450 or OBoNT group in a 1 : 1 ratio using a computer-generated randomization schedule. The full analysis set (FAS) method includes all subjects available to obtain data regarding the analysis of primary efficacy endpoint after administration among subjects who administered the study medication at least once without violating inclusion/exclusion criteria. Investigators were blinded to medication type throughout the study. The per-protocol set (PPS) population excluded patients who violated the protocol and did not complete the study.

Study medication and reconstitution

Each vial of DWP450 and Botox® (Allergan Inc., Irvine, CA, USA) contained 100 U of BoNT-A, 0.5 mg of human serum albumin, and 0.9 mg of sodium chloride. All vials were reconstituted with 2.5 ml of 0.9% sterile, non-preserved saline solution for a final dilution of 4 U/0.1 ml.

Treatment

Using a 30-gauge needle, study medication was intramuscularly injected into five sites: the midline of the procerus muscle, the inferomedial aspect of each corrugator muscle, and the superior middle aspect of each corrugator (at least 1 cm above the bony orbital rim; Fig. 1). The total injection volume was 0.5 ml (20 U); the dose per injection was 4 U. After the injections, all subjects were evaluated in clinic at weeks 4, 8, 12, and 16. At each visit, the investigator and the patient assessed the efficacy and safety of treatment. Photographs of each patient were taken at each visit using the same camera (EOS600D; Canon, Tokyo, Japan) and identical settings and lighting.

Clinical outcome measures

Patients were evaluated at weeks 0 (baseline), 4, 8, 12, and 16. Investigators assessed the glabellar line severity during every visit, both at maximum frown and at rest, using a four-point scale for glabellar lines according to a previously published study.[6] The primary efficacy endpoint was the responder rate at maximum frown at week 4. Responder rate was defined as the percentage of subjects with a score of none (0) or mild (1). Secondary efficacy endpoint measures included: (i) responder rate at maximum frown at weeks 8, 12, and 16; (ii) investigator-assessed glabellar lines responder rate at rest at weeks 4, 8, 12, and 16; (iii) responder rate at maximal frown and at rest at weeks 4, 8, 12, and 16 using photograph assessment; and (iv) participant-assessed degree of satisfaction and response rate of glabellar lines at weeks 4, 8, 12, and 16.

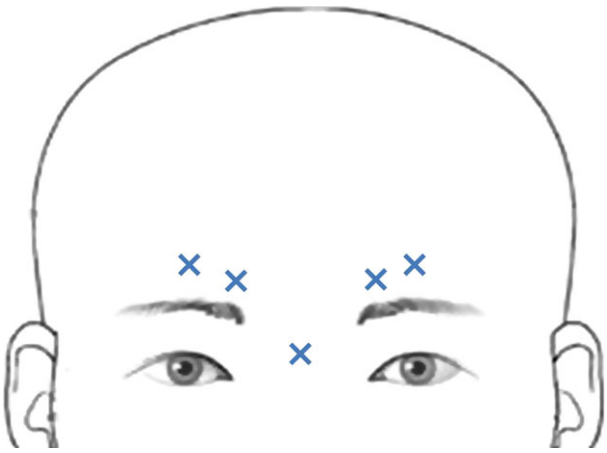

Figure 1 Injection sites

To ensure consistency of the scores across study centers, a photo guide, including example photos of each glabellar line rating, was provided for each facility. The photo guide was based on previously reported literature.[6] Three blinded independent investigators conducted photographic assessment, and all the blinded raters additionally received training in the use of the photo guide.

Subject-assessed degree of improvement was graded using the following nine-point scale: −4 = very markedly worse, ~100%; −3 = markedly worse, ~75% worse; −2 = moderately worse, ~50% worse; −1 = slightly worse, ~25% worse; 0 = no change; 1 = mild improvement, ~25% improvement; 2 = moderate improvement, ~50% improvement; 3 = marked improvement, ~75% improvement; 4 = complete improvement, ~100% improved. Participant satisfaction was assessed using the following seven-category scale: 1 = very dissatisfied, 2 = dissatisfied, 3 = somewhat dissatisfied, 4 = indifferent, 5 = somewhat satisfied, 6 = satisfied, 7 = very satisfied.

Safety assessments

To evaluate safety, patients were asked using non-leading questions at each follow-up visit about any symptoms or unexpected events that had occurred since the previous clinic visit. Adverse events (AEs) were monitored throughout the study, with physicians rating each occurrence in terms of severity, seriousness, and relationship to study treatment.

Botulinum toxin A antibody testing was performed using a mouse protection assay. Blood sampling was conducted both at baseline and at the final visit. Results of this bioassay were reported as either positive or negative.

Statistical analysis

The efficacy endpoint was analyzed in both FAS and PPS populations, and the safety endpoint was analyzed in safety population. Patients who committed protocol violations were excluded from the PPS analysis for overall response. PPS1 and PPS2 were defined as the analysis populations for the primary and secondary efficacy endpoint, respectively. To evaluate the primary efficacy endpoint, the lower limit of the 97.5% one-sided confidential interval (CI) was calculated. Additionally, the non-inferiority margin was defined as 15% ($\Delta = 0.15$), so that the study medication would be considered non-inferior if the lower limit of the CI for the difference between the two medications was greater than Δ. To assess the secondary efficacy endpoint, the chi-squared test or Fisher's exact test was performed. A two-sample *t*-test or Wilcoxon rank sum test was also performed to assess the subject degree of satisfaction.

Results

Patient population

Table 1 shows the study population according to the statistical set, and Figure 2 presents the flow and disposition of the participants. Of the 281 subjects screened, 268 were randomized, so that 135 were assigned to the DWP450 group and 133 to the OBoNT group. Of these, 263 completed the study, so that 265 of 268 randomized subjects composed the FAS population. The PPS1 population consisted of 263 subjects, excluding two patients who violated the visit window period and had committed concomitant medication violations. PPS2 population consisted of 245 patients, 18 of whom were excluded for the following reasons: eight for visit window violations, six

Table 1 Number of subjects according to statistical set

	DWP450	OnaboulinumtoxinA	Total
Randomized	135	133	268
Efficacy population			
Full analysis set	133	132	265
Per-protocol set 1[a]	131	132	263
Per-protocol set 2[b]	124	121	245
Safety populations	135	133	268

[a]Analysis population for primary efficacy endpoint.
[b]Analysis population for secondary efficacy endpoint.

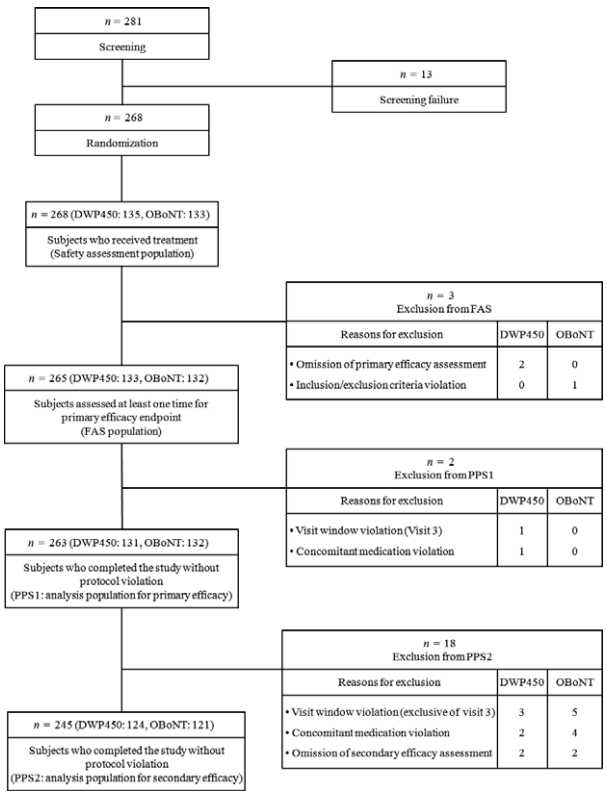

Figure 2 Flow of patients throughout the study. FAS, full analysis set; *n*, number of patients; OBoNT, onabotulinumtoxinA; PPS1, per-protocol set 1; PPS2, per-protocol set 2

for concomitant medication violations, and four for omissions of secondary efficacy endpoint assessment.

At baseline, the proportion of subjects who had moderate or severe glabellar lines at maximum frown was similar between the DWP450 (38.35% moderate and 61.65% severe) and OBoNT (39.39% moderate and 60.61% severe) groups (Table 2). The glabellar lines at rest also were similar in severity between the DWP450 (38.35% mild, 19.55% moderate, and 42.11% severe) and OBoNT (35.61% mild, 21.21% moderate, and 43.18% severe) groups.

Investigators' assessment

Clinical improvement in glabellar lines was shown for both groups (Figs. 3 and 4). The mean investigator-assessed glabellar line severity reached a nadir at week 4 in both treatment groups. Thereafter, the scores increased gradually (Fig. 5). Four weeks after treatment, the responder rate at maximum frown for the PPS1 population was 93.89% (95% CI: 89.79, 97.99) in the DWP450 group and 88.64% (95% CI: 83.22, 94.05) in the OBoNT group (Table 3). The lower limit of the 97.5% one-sided CI (– 1.53%) exceeded – 15%, which was defined as the margin of non-inferiority. For the FAS analysis, the responder rate was 93.98% for the DWP450 group (95% CI: 89.94, 98.03) and 88.64% for the OBoNT group (95% CI: 83.22, 94.05). The lower limit of the 97.5% one-sided CI (– 1.41%) exceeded – 15%.

The investigator-assessed responder rates for the DWP450 group in the PPS2 population at maximum frown were 93.55, 83.87, 75.61, and 62.10% at weeks 4, 8, 12, and 16, respectively. In the OBoNT group, the responder rates at maximum frown were 89.26, 82.64, 70.00%, and 54.55% at weeks 4, 8, 12, and 16, respectively (Table 4). At rest, the investigator-assessed responder rates were lower than those at maximum frown (73.39, 66.94, 66.67, and 67.74% for the DWP450 group and 68.60, 71.07, 71.67, and 68.60% for the OBoNT group at weeks 4, 8, 12, and 16, respectively).

The evaluation of glabellar lines based on photographs by blinded independent raters showed similar results to face-to-face assessment by investigators in both treatment groups (Table 4). However, the responder rate evaluated by blind rater photograph assessment was higher than that of face-to-face live assessment.

Table 2 Patient characteristics and baseline glabellar line severity at maximum frown and rest

	DWP450 (*n* = 133)	OnaboulinumtoxinA (*n* = 132)	Total (*n* = 265)
Patients characteristics			
Mean age (standard deviation)	47.82 (9.15)	47.31 (8.57)	47.57 (8.85)
P value[a]			0.45
Sex, *n* (%)			
Male	27 (20.30)	21 (15.91)	48 (18.11)
Female	106 (79.70)	111 (84.09)	217 (81.89)
P value[b]			0.35
Previous botulinum toxin exposure, *n* (%)			
Naïve	109 (81.95)	109 (82.58)	
Not naïve	24 (18.05)	23 (17.42)	
P value[b]			0.89
Initial severity of glabellar lines at maximum frown, *n* (%)			
Moderate	51 (38.35)	52 (39.39)	103 (38.87)
Severe	82 (61.65)	80 (60.61)	162 (61.13)
P value[b]			0.86
Initial severity of glabellar lines at rest, *n* (%)			
Mild	51 (38.35)	47 (35.61)	98 (36.98)
Moderate	26 (19.55)	28 (21.21)	54 (20.38)
Severe	56 (42.11)	57 (43.18)	113 (42.64)
P value[b]			0.89

[a]Difference between treatment groups (Wilcoxon rank sum test).
[b]Difference between treatment groups (chi-squared test).

Patients' assessment

The response patterns based on patient assessment using a nine-grade scale were similar to the investigator's assessment. Patients who scored more than two points (moderate improvement) were defined as improved. The responder rate for glabellar lines in the DWP450 group was 95.16, 91.94, 91.87, and 84.68% at week 4, 8, 12, and 16, respectively. The corresponding responder rate among the OBoNT group was 92.56, 94.21, 87.50, and 82.64% at week 4, 8, 12, and 16, respectively (Fig. 6). No significant differences between the two groups were observed at any time point.

Patients who scored more than six points (satisfied or very satisfied) were considered satisfied with the treatment. Satisfaction rate peaked at week 4 throughout week 8 then gradually declined over weeks 12 and 16 (Fig. 7). No statistically significant differences between the two groups were observed at any point in time.

Safety assessment

Of all 268 patients who received the treatment, 80 AEs from 51 subjects were reported during the study. The incidence of AEs was 20% (27 of 135; 44 AEs) in the DWP450 group and 18.05% (24 of 133; 36 AEs) in the OBoNT group. No statistically significant difference in the incidence of AEs between the DWP450 and OBoNT group ($P = 0.68$) was observed. Almost all AEs reported here were considered mild, though four moderate AEs – one (acute pyelonephritis) in the DWP450 group and three (headache, lumbar radiculopathy, tremor) in the OBoNT group – were reported. Furthermore, one serious

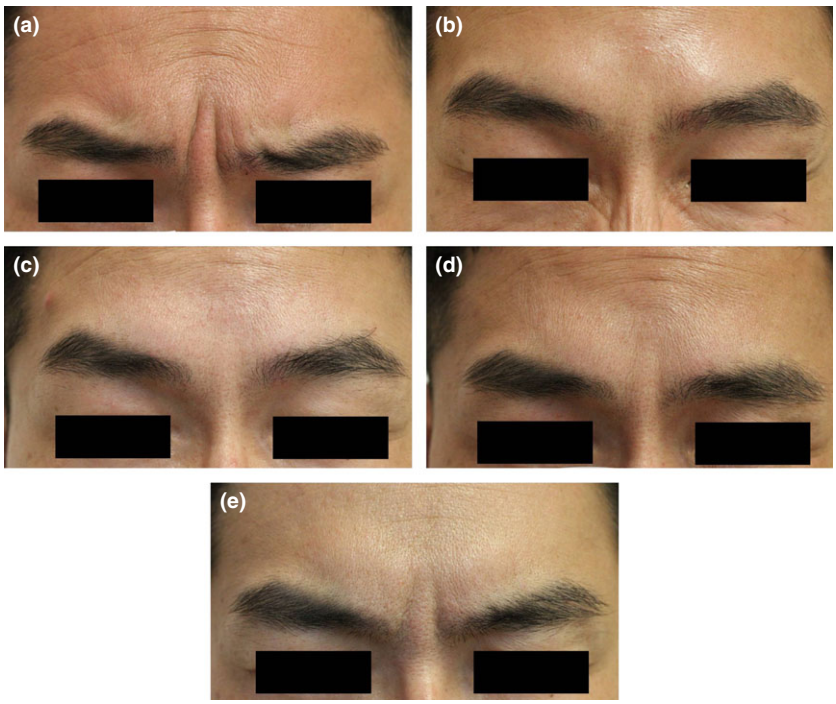

Figure 3 Representative photographs of glabellar lines at maximum frown in patient injected with DWP450 at (a) baseline, (b) week 4, (c) week 8, (d) week 12, and (e) week 16

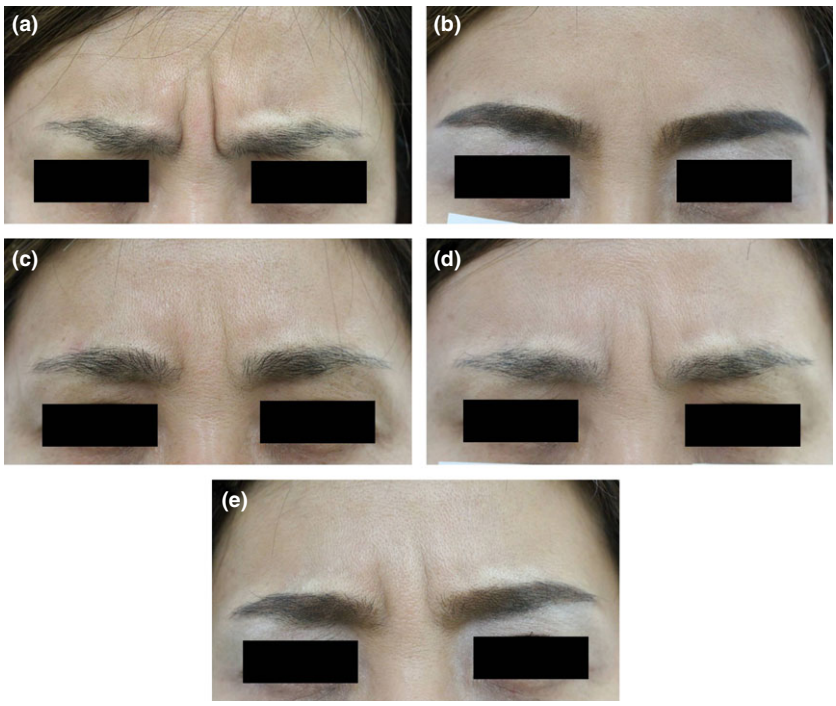

Figure 4 Representative photographs of glabellar lines at maximum frown in patient injected with onabotulinumtoxinA at (a) baseline, (b) week 4, (c) week 8, (d) week 12, and (e) week 16

AE (lumbar radiculopathy) occurred in the OBoNT group (one of 133; 0.75%), though the difference did not reach statistical significance ($P = 0.50$).

The incidence of AEs, for which the causal relationship with treatment could not be excluded, was 5.93% (eight of 135; 10 AEs) in the DWP450 group and 4.51% (six of 133; eight AEs) in the OBoNT group, which was not statistically significant ($P = 0.60$). All of the reported 18 AEs were mild and resolved without any complications. All 263 patients underwent botulinum toxin A antibody testing at both the initial and final visits, though no positive results occurred.

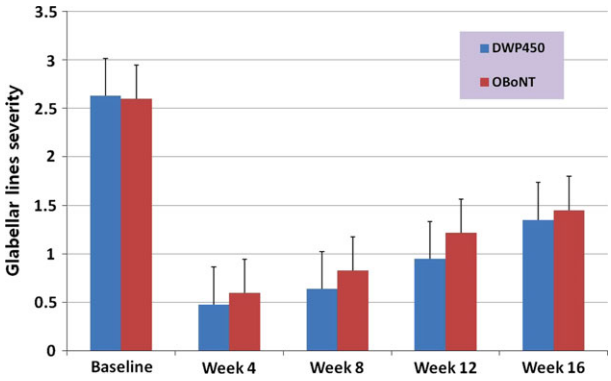

Figure 5 Changes in physician-rated glabellar lines severity at maximum frown. After injection of DWP450 or OBoNT, the mean scores were reduced at week 4. OBoNT, onabotulinumtoxinA

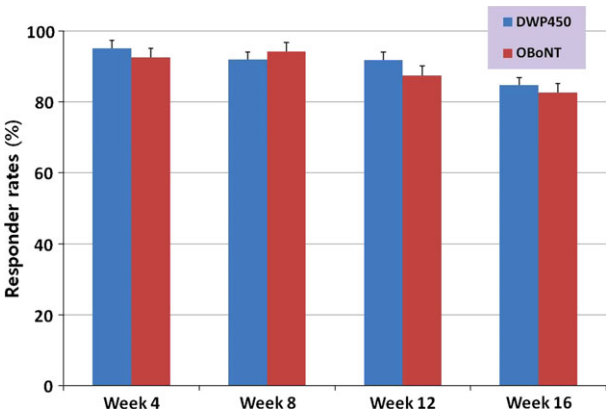

Figure 6 Percentage of responder rate based on patient self-assessment. OBoNT, onabotulinumtoxinA

Table 3 Primary efficacy endpoint assessment: Responder rate at maximum frown in two treatment groups for per protocol set 1 at week 4

Week 4	DWP450 (n = 131)	OnaboulinumtoxinA (n = 132)
Responder, n (%)	123 (93.89)	117 (88.64)
Two-sided 95% confidence interval	(89.79, 97.99)	(83.22, 94.05)
Difference between treatment groups		5.26
Lower limit of one-sided 97.5% confidence interval		− 1.53
Non-inferiority (margin = − 15.0%)		Yes

Discussion

Glabellar frown lines are considered cosmetically undesirable, as they can create an impression of more advanced age, anger, or worry.[7] Such rhytides may result from an overactivity of underlying muscles, including procerus, corrugator supercilii, and orbicularis oculi. Various treatment modalities, such as injections of filler, collagen, or autologous fat, surgical lifting, and laser resurfacing, have been used to improve facial wrinkles, though none addresses underlying muscle overactivity.

BoNT-A is a neurotoxin used cosmetically in the glabellar region to decrease rhytides. Injections of BoNT-A directly into the targeted muscle results in a local,

Table 4 Secondary efficacy endpoint assessment: Responder rates based on investigator's assessment using face-to-face and photographic evaluation for per protocol set 2

	DWP450 (n = 124)		OnaboulinumtoxinA (n = 121)	
	Face-to-face assessment	Photographic assessment	Face-to-face assessment	Photographic assessment
Week 4				
Responder at maximum frown	93.55	95.16	89.26	94.21
Responder at rest	73.39	78.23	68.60	78.51
Week 8				
Responder at maximum frown	83.87	90.32	82.64	88.43
Responder at rest	66.94	76.61	71.07	80.17
Week 12				
Responder at maximum frown	75.61	82.11	70.00	77.50
Responder at rest	66.67	73.98	71.67	79.17
Week 16				
Responder at maximum frown	62.10	71.77	54.55	68.60
Responder at rest	67.74	72.58	68.60	73.55

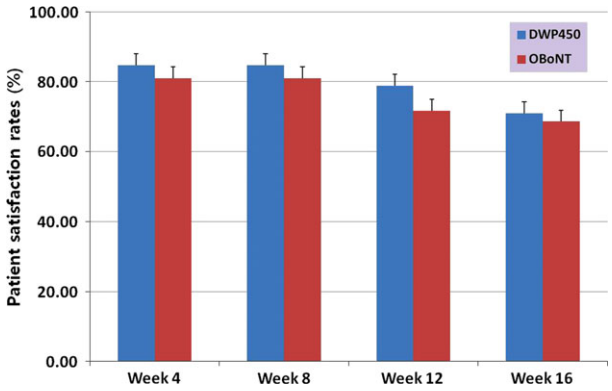

Figure 7 Patient satisfaction rate. OBoNT, onabotulinumtoxinA

selective reduction of muscle contraction by inhibiting the acetylcholine release from the terminal nerve to the muscle fiber.[8] Owing to the associated efficacy, botulinum neurotoxin preparations have been used therapeutically for over 20 years, with a number of clinical trials published detailing the efficacy and safety of these agents in facial aesthetics.[9]

This is the first double-blinded, randomized, phase III study comparing DWP450 and OBoNT in the treatment of glabellar lines. In this study, we demonstrate that DWP450 is similar to OBoNT in both primary and secondary efficacy endpoints. DWP450 showed a statistically significant efficacy in treating glabellar frown lines and was demonstrated to be non-inferior when compared with OBoNT. Furthermore, the overall results of this study indicate that the two study medications did not differ significantly with regard to several endpoints.

Since its FDA approval for the treatment of glabellar lines in 2002, OBoNT has been studied in various clinical studies. Similar responder rates have been previously reported in three randomized, double-blind controlled studies conducted in East Asian populations.[10–12] In those studies, the investigator-assessed responder rates were 88.6, 94.1, and 94.5% at maximum frown four weeks after treatment. In the current study, response rates peaked at week 4 (93.89 and 88.64%) in both BoNT-A groups and are comparable with previously reported studies.

The percentage of subjects with AEs was similar between the DWP450 (20.00%) and OBoNT (18.05%) groups, with no differences noted in the frequency of AEs. The majority of reported AEs were rated as mild in severity. No new safety concerns were identified, and the adverse reactions reported here were similar to those previously reported in the literature. According to one US study, most commonly reported to the FDA were lack of effect, injection site reaction (edema, pain, and bruise), and ptosis.[13] In our study, periorbital AEs – including ptosis and elevation of one or both sides of the lateral portion of the eyebrow – were the most frequent in both treatment groups. Periorbital related AEs might result from local diffusion, direct neurotoxin effect, and technique variability.

There is a possibility that development of antibodies against the neurotoxin may occur because botulinum toxins consist of foreign proteins. The formation of such neutralizing antibodies against the toxin may block BoNT-A action, resulting in partial or total antibody-induced treatment failure.[14,15] In our study, BoNT-A antibodies were not detected in either the DWP450 or OBoNT group. This result indicates that both medications are safe for treatment of glabellar lines.

The present study has notable limitations. First, this study did not assess the duration of effect to return to baseline or the previous 16 weeks, as the times returning to pretreatment wrinkle severity (relapse rates) were not included. In most cases, the duration of effect typically ranges between three and four months at a minimum, though it can be longer with repeated injections.[16] Studies with a longer follow-up period are clearly needed to evaluate the duration of effect. Second, the present study did not consider an individual glabellar contraction pattern. Despite similar facial anatomy, each individual may use his muscle differently.[17] Previous studies had identified several glabellar contraction patterns.[18,19] Classifying glabellar wrinkles can allow accurate treatment with botulinum toxin, reducing AEs.

In conclusion, this controlled study demonstrated that DWP450 represents a new agent that is both effective and safe for the treatment of glabellar rhytides. Used at the same dose as OBoNT, DWP450 was sufficient to reduce the severity of glabellar lines, and the responder rate was similar to that of OBoNT. No major differences between the two study medications were observed in this study.

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